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(71) Applicant (*for all designated States except US*): **THE UNIVERSITY OF BRITISH COLUMBIA [CA/CA]; Industry Liaison Office, 103 - 6190 Agronomy Road, Vancouver, British Columbia V6T 1Z3 (CA).**

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **ABBOTT, Frank, Slade [CA/CA]; 3919 W. 13th Avenue, Vancouver, British Columbia V6R 2T1 (CA). KARAGIOZOV, Stoyan, Kostadinov [CA/CA]; 2619 Ontario Street, Vancouver, British Columbia V5T 2Y1 (CA).**

(74) Agents: **LAW, Grace, S. et al.; Oyen Wiggs Green & Mutala, Suite 480 - The Station, 601 West Cordova Street, Vancouver, British Columbia V6B 1G1 (CA).**

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(54) Title: **VALPROIC ACID ANALOGUES AND PHARMACEUTICAL COMPOSITIONS THEREOF**

(57) Abstract: Analogues of valproic acid useful in treating neuroaffective disorders including convulsions, bipolar disorder, and migraine headache are disclosed. The analogues are halide substituted analogues, cyclic analogues, and conjugated diene analogues of valproic acid. Pharmaceutical compositions or prodrugs containing the analogues or pharmaceutically acceptable salts thereof are disclosed. Methods of making the compounds and treating mammals with neuroaffective disorders are also disclosed.

## INTERNATIONAL SEARCH REPORT

International Application No  
PCT/CA 03/01960

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	C07C53/21	C07C53/23	C07C57/02	C07C57/52	C07C57/26
	C07C59/21	C07C59/135	A61K31/185	A61P25/00	

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	PALATY, JAN ET AL: "Structure-Activity Relationships of Unsaturated Analogs of Valproic Acid" JOURNAL OF MEDICINAL CHEMISTRY , 38(17), 3398-406 CODEN: JMCMAR; ISSN: 0022-2623, 1995, XP002289407 cited in the application table 1; compounds 9,10	1-5,21, 22,25, 26,28,29
X	LEE, RONALD D. ET AL: "Stereoselective synthesis of the diunsaturated metabolites of valproic acid" JOURNAL OF PHARMACEUTICAL SCIENCES , 78(8), 667-71 CODEN: JPMSAE; ISSN: 0022-3549, 1989, XP001189684 cited in the application page 669 - page 670	1-5,21, 22,25, 26,36
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 Further documents are listed in the continuation of box C. Patent family members are listed in annex.

## \* Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the International filing date but later than the priority date claimed

- \*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- \*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- \*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- \*&\* document member of the same patent family

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Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
NL - 2280 HV Rijswijk  
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
Fax (+31-70) 340-3016

Authorized officer

Bonnevalle, E

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/01960

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DREIDING, ANDRE S. ET AL: ".alpha.- and .gamma.-Additions in the Reformatskii reaction with methyl gamma-bromocrotonate" JOURNAL OF THE AMERICAN CHEMICAL SOCIETY , 75, 3717-23 CODEN: JACSAT; ISSN: 0002-7863, 1953, XP002289408 page 3720, column 2; compound VII	1,2,4, 25,27, 35,36
X	TANG, WEI ET AL: "Fluorinated Analogs as Mechanistic Probes in Valproic Acid Hepatotoxicity: Hepatic Microvesicular Steatosis and Glutathione Status" CHEMICAL RESEARCH IN TOXICOLOGY , 8(5), 671-82 CODEN: CROTOEC; ISSN: 0893-228X, 1995, XP002289409 cited in the application page 672, column 2	1-3,5, 22-24
X	HAUCK, RALF SIEGBERT ET AL: "The enantiomers of the valproic acid analog 2-n-propyl-4-pentyanoic acid (4-yn-VPA): asymmetric synthesis and highly stereoselective teratogenicity in mice" PHARMACEUTICAL RESEARCH , 9(7), 850-5 CODEN: PHREEB; ISSN: 0724-8741, 1992, XP008032113 cited in the application page 851 - page 852	1-3,5, 22-24
X	US 2002/156320 A1 (NAU HEINZ) 24 October 2002 (2002-10-24) cited in the application the whole document	1,2, 22-24,36
X	TAKEUCHI, YOSHIO ET AL: "The first general and efficient method for the synthesis of tertiary alkyl fluorides" JOURNAL OF ORGANIC CHEMISTRY , 58(13), 3483-5 CODEN: JOCEAH; ISSN: 0022-3263, 1993, XP002289410 page 3484; compounds 2L,8L	1,2, 22-24,36
X	MYERS, ANDREW G. ET AL: "Synthesis of tertiary alkyl fluoride centers by asymmetric C-C(F) bond formation" TETRAHEDRON LETTERS , 38(40), 7037-7040 CODEN: TELEAY; ISSN: 0040-4039, 1997, XP004090413 page 7040; table 1	1,2, 22-24,36
		-/-

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 03/01960

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 94/06743 A (NAU HEINZ ; BOJIC URSULA (DE); HAUCK RALF SIEGBERT (DE); ELMAZAR MOHAM) 31 March 1994 (1994-03-31) claims -----	1,2,23, 24,28,29
X	ZHU, GUI-DONG ET AL: "Intramolecular Diels-Alder reaction of 8- trifluoromethyl -1,3,8-nonatrienes: an access to angular trifluoromethylated hydrindenes" BULLETIN DES SOCIETES CHIMIQUES BELGES , 103(5-6), 263-71 CODEN: BSCBAG; ISSN: 0037-9646, 1994, XP008032118 page 265, column 1 -----	1,20, 22-25

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/CA 03/01960

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**Although claims 30, 33, 34, 39, 40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: 35 because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:  
**see FURTHER INFORMATION sheet PCT/ISA/210**
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

### Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 30,33,34,39,40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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Continuation of Box I.2

Claims Nos.: 35

The scope of claim 35, in as far as the expression prodrug is concerned, is so unclear (Article 6 PCT) that a meaningful international search is impossible with regard to this expression. Nevertheless the search was complete for the prodrug as recited in claims 36-38.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

## INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 03/01960

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
US 2002156320	A1	24-10-2002	NONE		
WO 9406743	A	31-03-1994	DE AT AU AU CA WO DE DK EP ES GR HK JP JP KR NZ NZ US	4231085 A1 151067 T 683425 B2 4944293 A 2144419 A1 9406743 A1 59306054 D1 659172 T3 0659172 A1 2100558 T3 3023558 T3 1008016 A1 2887419 B2 8502045 T 244883 B1 255317 A 299727 A 5786380 A	17-03-1994 15-04-1997 13-11-1997 12-04-1994 31-03-1994 31-03-1994 07-05-1997 05-05-1997 28-06-1995 16-06-1997 29-08-1997 30-04-1999 26-04-1999 05-03-1996 15-02-2000 20-12-1996 24-11-2000 28-07-1998